REMARKS/ARGUMENTS

Claims 1-15, 17-53, 55-61 and 63 are pending in the application. Claims 42, 60 and 61 are allowed and claims 1-15, 17-41, 43-53, 55-59 and 63 are rejected.

In this Response claims 4, 38, 47, 56 and 61 (allowed) are cancelled without prejudice or disclaimer. Claims 1, 5, 42 (allowed), 45, 48 and 60 (allowed) are amended to clarify the features of applicants' method and composition. The claim amendments are all entirely supported by the application as originally filed and thus there is no issue of new matter. Entry of the claim cancellations and amendments is, thus, respectfully requested. Upon such entry, claims 1-3, 5-15, 17-37, 39-46, 48-53, 55, 57-60 and 63, as amended, will be remaining in the application for the Examiner's review and consideration. Reconsideration of the application is respectfully requested.

Allowable Claims

Applicants note with appreciation the Examiner's statement in ¶10 on p. 9 of the Action that claims 42, 60 and 61 are allowed. For purposes of clarifying the features of the composition(s) recited in the subject claims, however, applicants have herein amended claims 42 and 60. Furthermore, claim 61 has been cancelled without prejudice or disclaimer from the application. Claims 42 and 60, as amended, are still believed to be in a condition for allowance since the claim amendments are simply offered to make explicit that which is already implicitly taught in the application. Applicants, furthermore, expressly reserve the right to separately pursue patent protection for the subject matter of canceled claim 61.

Claim Rejections Under 35 U.S.C. §103

In ¶3 on p. 2 of the Office Action, claims 1-8, 12-15, 17-41, 43-47, 49-51, 55-59 and 63 are rejected under 35 U.S.C. §103 over Stern et al. (USP 6,086,918) in view of Habener (USP 5,120,712) or Balschmidt et al. (USP 5,157,021) or Barbier et al. (USP 6,110,892) or European Patent Application No. 0 878 201 (Tamura et al.) or Neiss et al. (USP 4,804,742), i.e., for the reasons set forth on pp. 2-3 of the Office Action. Claims 5, 38, 47 and 56 have, as indicated above, been canceled from the application without prejudice or disclaimer. Thus the rejection is moot as to those claims. The rejection is respectfully traversed as it relates to the remaining claims.

Of the rejected claims, nos. 1 and 45 are written in independent form. These claims have been amended, furthermore, to more clearly recite, respectively, the novel and non-obvious features of applicants' composition and method. As now amended, claim 1 reads as follows:

> An oral pharmaceutical composition for delivery of a physiologically active peptide agent that is not naturally amidated at its C terminus, said composition comprising a therapeutically effective amount of said active peptide, wherein the active peptide has an amide group added at its C terminus, and an absorption enhancer effective to promote bioavailability of said active agent.

Additionally, as amended claim 45 now reads as follows:

> A method for enhancing the bioavailability of an orally delivered physiologically active peptide agent comprising: (a) amidating a peptide agent that is not naturally amidated at its C-terminus at said C-terminus; and (b) orally administering said amidated peptide agent in combination with at least one absorption enhancer effective to promote bioavailability of said active peptide agent.

According to the discussion of the bases of the rejection, i.e., as set forth in ¶3 of the Office Action, Stern et al. is cited due to its teaching with regard to the oral administration of peptides such as insulin, salmon calcitonin, parathyroid hormone and lhrf using a carrier comprising a pH-lowering agent, an absorption enhancer, a non-physiologically active protein, a gelatin capsule and an enteric coating. Further according to the Office Action, Stern et al. do not teach peptides which are amidated GLP-1 analogs, amidated insulin analogs or amidated PTH analogs. Thus, in order to supply the element missing from Stern et al. of a peptide that is amidated at a location that is not naturally amidated, the Examiner has combined Stern et al. with one from a variety of 'secondary' references (as identified above) and submits that it would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to administer the peptides disclosed in such secondary references in the formulation taught for use in Stern et al. Applicants respectfully disagree, however, for the reasons set forth below.

As indicated above, the claims (esp. claims 1 and 45) have been amended to more clearly recite applicants' composition and method. As now constituted, claim 1 for example is directed to an oral pharmaceutical composition comprising a physiologically active peptide agent not naturally amidated at its C-terminus which, wherein the agent has an amide group added at such

C-terminus and wherein the amidated agent is orally administered together with an absorption enhancer effective to promote bioavailability of the active agent. These same features are, of course, included in all of the claims that depend, whether directly or indirectly, from the amended claim 1. In like manner claim 45, directed to a method for enhancing the bioavailability of an orally delivered physiologically active peptide agent, wherein the method as now claimed comprises the steps of: (a) amidating a peptide agent that is not naturally amidated at its C-terminus at said C-terminus; and (b) orally administering the amidated peptide in combination with an absorption enhancer effective to promote bioavailability of said active peptide agent. The claims depending from the subject method claim, in the same manner as those depending from claim 1, also include all of these features as recited in claim 45.

With the above, modified claim language taken into account, applicants submit that Stern '918 does not disclose a physiologically active peptide not amidated at its C-terminus wherein the peptide has an amide group intentionally added to its C-terminus, and especially not wherein such amidation leads to an enhancement in the bioavailability of a composition comprising the amidated peptide together with an absorption enhancer effective to promote the bioavailability of the active peptide. As to the 'secondary' references cited by the Examiner in combination with Stern et al. in an effort to render the claims obvious, notwithstanding that they may contain a teaching regarding peptides that are amidated at a location where such peptides are not naturally amidated, applicants submit that these references do not teach or suggest to a skilled artisan working in this field to take a peptide that is not naturally amidated at its C-terminus and to add an amide group thereto, i.e., at such C-terminus, particularly for the purpose of enhancing the bioavailability of the resultant amidated peptide in the case where the peptide is, specifically, orally delivered.

The above discussed features are specifically recited in claims 1-45 and, thus, those claims and the claims depending from those claims are believed to be not obvious over the references combined in the subject rejection. The Examiner is, therefore, respectfully requested to reconsider and withdraw the rejection of applicants' claims 1-8, 12-15, 17-41, 43-47, 49-51, 55-59 and 63 under 35 U.S.C. §103.

In ¶4 of the Office Action claims 5 and 48 are rejected under 35 U.S.C. §103 over the references applied above in the rejection of claims 1-8, 12-15, 17-41, 43-47, 49-51, 55-59 and

63 and further in view of Stern et al. U.S. Patent No. 5,912,014. This rejection is traversed as well.

Rejected claims 5 and 48 depend, respectively, from claims 1 and 45 and thus they include all of the features recited in their respective parent claim. Applicants submit that they have demonstrated above that claims 1 and 45, and thus by extension also claims 5 and 48 since they also include the distinguishing features, are not obvious over the combination of U.S. Patent No. 6,086,918 to Stern et al. with one of Habener, Balschmidt et al., Barbier et al., the European patent application, or Neiss et al. Nor does the additional Stern et al. reference included within the combination, i.e., Stern et al. '014, remedy the deficiencies identified in the remaining members of the combination of art cited by the Examiner. That is, Stern et al. '014 is cited, as indicated at Office Action p. 4, due to its disclosure relating to the formation of salmon calcitonin made with a C-terminal glycine extension, which is enzymatically converted to an amide group. Even taking this disclosure at 'face value', however, when the reference is combined with Stern et al. '918 and any of the secondary references discussed above, the proposed combination still neither teaches nor even suggests a physiologically active peptide that is not amidated at its C-terminus wherein the peptide then has an amide group added at such C-terminus, and especially not where such amidation leads to an enhancement in the bioavailability of the amidated peptide when such peptide is administered together with an absorption enhancer that is effective to promote the bioavailability of the peptide.

Based on the reasoning set forth above, therefore, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 5 and 48 under 35 U.S.C. §103.

Further to the above, in §5 of the Office Action claims 1-15, 17-41, 43-47, 49-53, 55-59 and 63 are rejected under 35 U.S.C. §103 over WO 02/043767 of Unigene Laboratories, Inc. in view of Habener, or Balschmidt et al., or Barbier et al., the European patent application No. 0 878 201 or Neiss et al. Of these rejected claims, nos. 4, 38, 47 and 56 are canceled from this application without prejudice or disclaimer and thus the rejection is moot as to those rejected claims. As regards those claims still pending, however, the rejection is respectfully traversed.

This rejection is similar in many respects to the rejection of claims 1-8, 12-15, 17-41, 43-47, 49-51, 55-59 and 63 under §103 discussed above, i.e., wherein the primary reference is U.S. Patent No. 6,086,918 rather than, as it is in the present case, International Publication No.: WO 02/043767. As noted in the portion of the Office Action bridging pp. 4-5 of the Office Action,

the WO '767 publication is cited due to its disclosure with regard to the oral administration of peptides such as insulin, salmon calcitonin, parathyroid hormone, lhrf and GLP-1 linked to a membrane translocator using a carrier comprising a pH-lowering agent, a protease inhibitor, an absorption enhancer, a non-physiologically active peptide, a gelatin capsule and an enteric coating. The 'secondary' references, i.e., Habener, Balschmidt, et al. etc., are cited for the same reasons as in the rejection discussed above, i.e., due to their disclosure of a peptide that is amidated at a location that is not naturally amidated.

However, the combination of WO 02/043767 (Unigene Laboratories, Inc.) with one of the secondary references does not bring one any closer to the composition and method as now recited in, e.g., claims 1 and 45 than does the combination of Stern et al. '918 with such secondary reference(s). That is, even taking the Examiner's description of the content set forth in the subject references at face value, the cited combinations both suffer from the same deficiencies in that they do not disclose, nor do they suggest to one having at least an ordinary level of skill in the relevant art, a physiologically active peptide that is not amidated at its C-terminus wherein the peptide then has an amide group added at such C-terminus, and especially not where such amidation leads to an enhancement in the bioavailability of the amidated peptide when such peptide is administered together with an absorption enhancer that is effective to promote the bioavailability of the peptide.

For the reasons set forth above, therefore, the Examiner is respectfully requested to reconsider and withdraw the rejection under 35 U.S.C. §103 of claims 1-15, 17-41, 43-47, 49-53, 55-59 and 63.

Again, in like manner to another rejection above, in ¶6 on Office Action pp. 6-7, claims 5 and 48 are rejected under 35 U.S.C. §103 over WO 02/043767 taken in combination with Habener, or Balschmidt et al., or Barbier et al., the European patent application No. 0 878 201 or Neiss et al. cited to reject claims 1-15, 17-41, 43-47. 49-53, 55-59 and 63 (see above), and further in view of Stern et al. '014. This rejection is also traversed by applicants.

Rejected claims 5 and 48 as noted above depend, respectively, from claims 1 and 45 and thus they include all of the features recited in their respective parent claim. Applicants submit that they have demonstrated above that claims 1 and 45, and thus by extension also claims 5 and 48 since they also include the distinguishing features, are not obvious over the combination of WO 02/043767 of Unigene Laboratories, Inc. with one of Habener, Balschmidt et al., Barbier et

al., the European patent application, or Neiss et al. Nor does the additional Stern et al. reference included within the combination, i.e., Stern et al. '014, remedy the deficiencies identified in the remaining members of the combination of art cited by the Examiner. That is, Stern et al. '014 is cited, as indicated at Office Action p. 6, due to its disclosure relating to the formation of salmon calcitonin made with a C-terminal glycine extension, which is enzymatically converted to an amide group. Even taking this disclosure at 'face value', however, when the reference is combined with WO 02/043767 and any of the secondary references discussed above, the proposed combination still neither teaches nor even suggests a physiologically active peptide that is not amidated at its C-terminus wherein the peptide then has an amide group added at such C-terminus, and especially not where such amidation leads to an enhancement in the bioavailability of the amidated peptide when such peptide is administered together with an absorption enhancer that is effective to promote the bioavailability of the peptide.

Based on the reasoning set forth above, therefore, the Examiner is also respectfully requested to reconsider and withdraw this rejection of claims 5 and 48 under 35 U.S.C. §103.

Claim Rejections Under 35 U.S.C. §102

In ¶7 on p. 7 of the Action, claims 1, 4, 5, 17-19 and 41 are rejected under 35 U.S.C. §102(b) as being allegedly anticipated by the Naugebauer et al. article (*Biochemistry*, Vol. 34, pps. 8835-8842). Of the rejected claims, no. 4 has been cancelled herein from the application without prejudice or disclaimer. Thus the rejection is moot as to this cancelled claim. As to the remaining claims, however, applicants respectfully traverse the rejection.

Of the rejected claims, only no. 1 is written in independent form. The remaining rejected claims all depend from claim 1, directly or indirectly, and thus they include all of the features recited in the independent claim. As discussed above, claim 1 in its presently amended state, reads as follows.

> An oral pharmaceutical composition for delivery of a physiologically active peptide agent that is not naturally amidated at its C terminus, said composition comprising a therapeutically effective amount of said active peptide, wherein the active peptide has an amide group added at its C terminus, and an absorption enhancer effective to promote bioavailability of said active agent.

In order for a reference to anticipate a claim the reference must disclose each and every element recited in the subject claim. In the case of the present rejection, however, applicants submit that the reference does not teach an oral pharmaceutical composition as presently claimed adapted for oral delivery of a physiologically active peptide agent that is not naturally amidated at its C-terminus, the composition comprising a therapeutically effective amount of the active peptide wherein the active peptide has an amide group added at its C terminus, and wherein the peptide is combined within the composition with an absorption enhancer effective to promote bioavailability of the active agent.

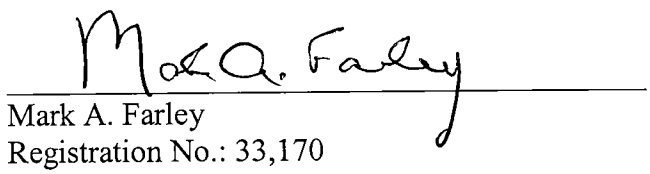
In light of the above, therefore, the Examiner is respectfully requested to reconsider and withdraw the rejection of the subject claims under 35 U.S.C. 102(b).

Summary

Applicants respectfully submit that the claim amendments and arguments presented herein are believed to be sufficient to overcome all of the rejections set forth in the present Office Action. The Examiner is, therefore, requested to withdraw the subject rejections and to issue a Notice of Allowance with regard to all of the remaining claims.

THIS CORRESPONDENCE IS BEING SUBMITTED ELECTRONICALLY THROUGH THE PATENT AND TRADEMARK OFFICE EFS FILING SYSTEM ON December 2, 2010.

Respectfully submitted,



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